



## Big Tobacco and the human genome: driving the scientific bandwagon?

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### Abstract

The tobacco industry first began to promote the idea that a minority of smokers are ‘genetically predisposed’ to lung cancer in the 1950s. We used tobacco industry documents available as a result of litigation to investigate the role of the tobacco industry in funding the ‘scientific bandwagon’ described by Fujimura, in which genetics has come to dominate the cancer research agenda. From 1990-1995 inclusive, 52% of the project funding allocated by British American Tobacco’s Scientific Research Group went to genetic research, mainly based in universities and at one cancer charity. The largest project involved a pharmacogenetic research unit, based in a UK medical school, which was established with the help of tobacco industry PR consultants in 1988. The unit received half its project funding from the industry in 1992. Its main aim was to identify a minority of smokers who are supposedly ‘genetically susceptible’ to lung cancer, so that smoking cessation measures could be targeted at them. This aim was adopted and promoted by influential scientists at the US National Institutes of Health and the UK Medical Research Council in the late 1980s, in the run up to the Human Genome Project.

BAT’s research funds were also used to counter claims by others to have identified a unique ‘genetic fingerprint’ for tobacco smoke in lung cancer cells. We conclude that the tobacco industry has played a significant role in shaping research agendas, in particular, by promoting the idea that individual genome screening would be of benefit to public health.

### Introduction

Tobacco smoking was responsible for an estimated 3 million deaths worldwide in 1990, predicted to rise to 10 million by 2030 if present trends continue.<sup>2,3</sup> The tobacco industry has a long history of funding research into the health effects of tobacco as part of a sophisticated legal and public relations strategy.<sup>4,5</sup> Its strategies on Environmental Tobacco Smoke (ETS) and nicotine have been discussed elsewhere<sup>6,7,8,9,10</sup> but we are not aware of any detailed examinations of its funding of human genetic research.

Fujimura (1988) describes a “scientific bandwagon”, which “exists when large numbers of people, laboratories and organizations commit their resources to one approach to a problem”.<sup>11</sup> She describes how, by 1984, molecular biological cancer research became a line of research that scientists increasingly joined in order to build successful careers. The bandwagon was driven by major investments in infrastructure and very large increases in funding allocations, particularly from the US National Institutes of Health (NIH).

However, the NIH were not the first or only funders active in this area. From 1954 to 1999 the Council for Tobacco Research (the CTR, formerly the Tobacco Industry Research Committee) was the main tobacco-industry-funded research body world-wide, and genetics played a central role in its \$20 million a year research programme.<sup>12</sup> By 1994, the CTR was one of the largest private funders of medical research in the USA and had awarded nearly \$225 million to approximately 1,000 researchers, sponsoring “pioneering work in identifying familial cancers, the role of genetic factors in cancer formation, and the identification of oncogenes”. Its first director, Clarence Cook Little, was a eugenicist who promoted the idea that there might be a gene that both leads people to smoke and predisposes them toward cancer, implying that the statistical link between smoking and lung cancer was not causal.<sup>13</sup> To support his position, Little used a 1957 paper by the British statistician and eugenicist Sir Ronald Fisher, published in the *British Medical Journal*.<sup>14</sup> In 1958, following a letter from Fisher to *Nature*,<sup>15</sup> the *New York Times* reported that Fisher was a “consultant statistician to the tobacco manufacturers”.<sup>16</sup>

Although Fisher’s theory no longer commands scientific support,<sup>17</sup> genetic predisposition to lung cancer is still a topic of active research. It is possible that such research may help to elucidate the molecular mechanisms underlying cancer. However, some researchers have also claimed that genetic screening will one day predict which smokers will get lung cancer, allowing smoking cessation measures to be targeted at this minority of individuals. Claims to have developed a genetic test which “apparently distinguishes cigarette smokers whose genes make them prone to lung cancer from those resistant to developing the malignant tumour” were first made in the *New York Times* in 1973,<sup>18,19</sup> by researchers who were seeking (and subsequently received) funding from the CTR.<sup>20,21</sup>

However, this hypothesis is not supported by twin studies, which suggest that lung cancer has no significant inherited genetic component and that therefore there is no possibility of a genetic screening test with high clinical utility.<sup>22,23,24</sup> Further, because many diseases are caused by smoking,<sup>25,26</sup> all smokers benefit from quitting, whatever genetic variants they have. Genetic testing in clinical practice would therefore provide no additional useful information for physicians and could mislead individuals about the risk of smoking.<sup>27</sup>

Hall *et al.* (2002) argue that the tobacco industry may have an interest in using the possibility of genetic screening for disease susceptibility to convince ambivalent smokers that they do not need to quit.<sup>28</sup> This theory is consistent with a 1996 memo from the director of media at PR firm Burson-Marsteller to Philip Morris, which puts the marketing case for the tobacco industry to undertake this type of research:

*“A simple test might eventually be devised to tell a smoker whether or not he is at risk. This would put the burden of any consequence from smoking on the individual, and would clear the way for the non-susceptible population to smoke with a clear conscience”.*<sup>29</sup>

Although the CTR ceased to exist in 1999, British American Tobacco (BAT) continued to fund academic research via its Scientific Research Group (SRG), including research on genetic predisposition to disease, until at least 2000.<sup>30</sup> We therefore set out to detail the role of the SRG in human genetic research, using BAT documents released as a result of litigation, supplemented with related documents released by the CTR and by Philip Morris. We aimed to identify what research had been funded and why, and the influence of the tobacco industry on the research agenda.

Whilst the tobacco industry may see promotion of genetic screening of smokers as advantageous to its business, it may perceive other genetic health research as a threat. In 1990, researchers began to link the pattern of damage in the p53 gene in lung cancer cells with benzo[a]pyrene, a constituent of tobacco smoke, and by 1996 Denissenko and colleagues had demonstrated an in-vitro effect.<sup>31,32,33</sup> The prospect of a unique ‘genetic fingerprint’ for tobacco smoke in lung cancer cells has implications for the financial liability of the tobacco industry. Bitten *et al.* (2005) investigated the tobacco industry’s response, showing that the industry conducted research which appeared to cast doubt on these findings.<sup>34</sup> Our research, which overlaps with theirs, also sheds some further light on these developments.

## Methods

Our primary sources were documents made publicly available as a result of past litigation settlements. In 2001, we visited the BAT depository at Guildford to identify the scientific research projects funded by BAT’s Scientific Research Group (SRG) during the 1990s. We used the search terms: “Scientific Research Group”; “SRG”; the names of the BAT employees responsible for the SRG (“Proctor” and “Boyse”); and, in secondary searches, the names of researchers and consultants funded by the SRG. We collected more than 800 documents in total during 10 days at the repository, including SRG meeting minutes, contracts, newsletters and notes of visits; grant proposals, reviewers comments and progress reports; BAT memos, notes and letters; and letters to BAT.

The document set is not comprehensive due to limitations in both the supply of documents and their indexing, and the difficult logistics of obtaining access to the documents at Guildford.<sup>35,36,37</sup> Making an exact catalogue of documents proved difficult, as documents with different Bates Numbers are sometimes copies of the same original and in some cases the distinction between single and multiple documents may be somewhat arbitrary. However, the SRG budgets we identified contain partial information for 1989, complete figures for 1990-1995 and projected figures for 1995-1997, allowing us to make an analysis of BAT’s research funding priorities from 1990-1995 (see supplementary material, S1).

To obtain a fuller picture we conducted additional searches of two further tobacco industry websites using the names of researchers and consultants: the Council for Tobacco Research USA, Inc. (the CTR)<sup>38</sup> and Philip Morris (PM).<sup>39</sup> We omitted researchers and consultants primarily involved in nicotine research or environmental tobacco smoke (ETS). Our search terms and a summary of the additional documents

we identified are given in Table 1. The presence of documents in the CTR and PM files does not necessarily indicate a link between the company and the named researcher. For example, documents may include copies of published papers; newspaper articles; notes on conference presentations; or research proposals that have been refused.

**Table 1: Summary of CTR and PM documents\*.**

Search term	Number of CTR documents	Number of Philip Morris documents
Idle JR	460	304
Daly AK	20 <sup>†</sup>	8 <sup>‡</sup>
Rothschild H	194	196
Springall A	1	467
Carter ND	None	None
Cooper DN	4	13
Currie G	1	5
Poulsen H	None	1
Clausen J	None	9
Stell PM	11	21
Field JK	None	13
Farmer P	None	47
Parry J	None	83
Feinstein A	108	1384

\* Documents relating to different individuals with the same name have been identified and omitted from these totals. Documents with different Bates Numbers are counted as distinct, even if they are copies of the same original. In some cases PM documents are copies of CTR documents.

<sup>†</sup> All but 2 overlap with Idle JR.

<sup>‡</sup> All but 3 overlap with Idle JR

By checking funding applications and their response, we established that two researchers (Idle and Rothschild) had received research funding from the CTR. A detailed analysis of these documents is included in this paper. Idle also received funding from Philip Morris, mainly for work on ETS which is largely omitted from this paper. The consultants J. Parry and A. Feinstein received funding from Philip Morris and from the CTR respectively. We used these documents to establish the extent of their tobacco industry links, but did not examine these projects in detail. Springall was a commercial consultant to BAT (not an academic researcher) so we did not investigate the PM documents listed in his name.

We then searched PubMed<sup>40</sup> for journal articles published by the researchers listed in Table 1 (omitting the consultants Feinstein and Parry). We used the documents to provide an overview of the SRG's aims, objectives and relationships with researchers and consultants; to quantify the cost and duration of each research project and the importance of genetics in the programme; and to examine funding declarations on journal articles. We also produced two detailed chronologies of the involvement of BAT-funded researchers in research on 'genetic susceptibility' to lung cancer and one on p53 mutations in lung cancer cells (see supplementary material, S2, S3 and S4),

and analysed the role of these researchers in the development of the scientific bandwagon described by Fujimura.

## Results

### *The SRG – aims and objectives*

BAT's Scientific Research Group (SRG) was formed in 1986.<sup>41</sup> A key objective was: "To maintain a detailed awareness of, and an ability to respond to, scientifically related regulatory issues that impact on cigarette use".<sup>42</sup> Research proposals were assessed by BAT not only for their scientific merit, but also for their contribution to the agreed strategic objectives of the BAT group. Future strategies for research were developed as issues arose and in 1993 gave particular emphasis to seeking "confounding factors" in the associations between both active and passive smoking and lung cancer and heart disease.<sup>43</sup> The SRG considered "genetic predisposition" to be one possible confounding factor, along with other factors such as diet.

### *Contracts*

BAT funded both consultants and researchers via the SRG. Researchers signed contracts with the British-American Tobacco Company Limited.<sup>44</sup> These contracts allowed them to publish at the sole discretion of themselves and their research institutes, but required them to send copies to BAT at least 28 days in advance. BAT reserved the right to terminate grants at any time if the research programme did not follow the proposal.

The consultants reviewed research proposals for the SRG. Although most were medical researchers based in universities, they signed contracts with BAT which committed them to safeguarding the "best interests of the Company".<sup>45</sup> In 1993, BAT's consultants on molecular biology and epidemiology respectively were Professor James Parry (University of Wales, Swansea) and Professor Alvan R. Feinstein (Yale).<sup>46,47</sup> Feinstein had a long history of involvement with tobacco industry research, including funding for "special projects" determined by tobacco industry lawyers.<sup>48,49,50,51</sup> Parry, who was receiving project funding from Philip Morris in 1998, was described as having a "long-standing relationship" with the company, and had recently applied for a new grant.<sup>52</sup> Both Parry and Feinstein were editors-in-chief of academic journals whilst employed as BAT consultants.

### *The SRG - funding priorities and journal publications*

The SRG budgets we obtained were complete for the period 1990-1995, as detailed in the supplementary material, S1. Most of the SRG's research budget during this period (60% or £1,570,600) was spent on projects based in UK universities and associated hospitals or research institutes, including one cancer charity. The remainder was spent on projects undertaken in overseas universities (26%) or by UK consultants (13%).

Whilst research on nicotine (24% of funding) and ETS (12% of funding) were clearly of high importance to BAT, genetic research, mainly into cancer, was more important - receiving 52% of the total £2.6 million allocated for 1990-1995.

Table 2 outlines the genetic research projects funded by the SRG for the period 1990-1995. Where indicated, projects extended before or after this six-year period, receiving additional funding. We have divided this genetic research broadly into two types:

- (i) research into whether some people are more genetically susceptible (or “predisposed”) to some diseases – particularly lung cancer - than others;
- (ii) research into the genetic damage caused by tobacco smoke and other factors, and the molecular mechanisms leading to cancer.

**Table 2: SRG Genetic Research Projects 1990-1995**

<b>Project</b>	<b>SRG Funding 1990-1995</b>	<b>Earlier/Later Funds</b>	<b>Institution</b>	<b>Lead Researcher (dates)</b>	<b>Number of publications acknowledging BAT-funding</b>
<b>Genetic susceptibility projects</b>					
Cytochrome P450 polymorphisms	£429,200	Yes	University of Newcastle Upon Tyne	Prof JR Idle ('89-'93) and Dr AK Daly ('94-'96)	Sixteen, <sup>53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68</sup>
Human genetics of lung cancer	£80,000	Yes	Louisiana State University, USA	Dr H Rothschild ('94-'96)	None identified
Segregation analysis	£72,700	No	None: Consultant	Dr A Springall ('91-'93)	None identified
DNA polymorphisms in hypertension	£36,500	Yes	St George's Hospital Medical School, London	Dr ND Carter ('87-'90)	None identified
<b>Genetic damage/mechanisms projects</b>					
Mutations in thrombotic disease	£154,700	Yes	Thrombosis Research Institute, London	Dr DN Cooper ('92-'95)	Four <sup>69,70,71,72</sup> ( plus one acknowledging “British-American PLC” <sup>73</sup> )
p53 and cell cycle	£141,700	Yes	Marie Curie Research Institute	Dr G Currie ('90-'93)	None identified
Oxidative DNA damage	£145,000	Yes	Copenhagen University, Denmark	Prof H Poulsen ('94-'96)	Four <sup>74,75,76,77</sup>



DNA adducts	£123,600	No	Roskilde University, Denmark	Prof J Clausen ('90-'93)	One <sup>78</sup>
p53 in head and neck cancer	£80,200	No	University of Liverpool	Prof PM Stell ('91) and Dr JK Field ('92-'93)	None identified.
DNA adducts and free radical damage	£60,000	Yes	MRC Toxicology Unit, Leicester	Dr P Farmer ('93-'96)	None identified
Review of cytokines	£11,000	No	Not known	Nelson ('95)	Not known

### *Journal publications*

Table 2 also shows the publications acknowledging BAT funding relating to each project.

The largest number of journal papers resulted from the project led initially by Professor Jeffrey Idle at the University of Newcastle upon Tyne, UK. Of the 16 papers by his research team listed in Table 2, six also acknowledge CTR funding and two acknowledge both the CTR and the Smokeless Tobacco Research Council (STRC, another tobacco-industry-funded body). Six additional papers<sup>79,80,81,82,83,84</sup> acknowledge support from the CTR and another three acknowledge the STRC.<sup>85,86,87</sup> Fourteen of these 25 tobacco-funded papers (12 with Idle's name on) were published in *Pharmacogenetics*. Idle was editor-in-chief of *Pharmacogenetics* from 1991 to October 1998,<sup>88,89</sup> a journal which he founded whilst receiving BAT funding.

For most of the projects we were unable to identify any journal papers acknowledging BAT funding.

### *Projects*

#### *Genetic susceptibility to lung cancer*

Research on genetic susceptibility to lung cancer received the most funding, confirming the tobacco industry's continued interest in this area of research. Jeffrey Idle's project was also the only project simultaneously funded by the CTR.<sup>90</sup> Chronologies for the projects involving Idle, Daly, Rothschild and Springall are provided in the supplementary material S1 and S2.

Idle informed the CTR in 1986<sup>91</sup> that his 1984 *Nature* paper on role of the CYP2D6 gene in metabolism of the drug debrisoquine and its link to risk of lung cancer "may herald a long-overdue change in the practice of epidemiology" and that he had established collaboration with the US National Institutes of Health (NIH) to pursue "the host factors which determine individual lung cancer risk". He joined the CTR's Scientific Advisory Board (SAB)<sup>92</sup> in July 1986. Statements to the press by the NIH in 1987, endorsing Idle's results and suggesting that genetic testing would allow

smoking cessation to be targeted at a minority of smokers, were regarded as “favorable publicity” by the industry.<sup>93,94</sup> This led to a presentation by Idle to the CTR Board (which included representatives of six tobacco companies, two legal firms and the CTR’s PR company) in December 1987.<sup>95,96</sup>

Within a month, CTR and BAT public relations advisors became involved in helping him establish a “Laboratory of Cancer Pharmacogenetics” in the UK.<sup>97</sup> The Pharmacogenetics Unit in the University of Newcastle Medical School, was “greatly expanded and revamped” to create a Chair for Idle. BAT’s chairman, Patrick Sheehy, was kept informed of progress.<sup>98,99,100,101</sup> The university received a five-year “research agreement” from BAT on Idle’s move there in September 1988.<sup>102</sup> In 1992, 50% of the project funding for “this and related research” at the unit was from the tobacco industry,<sup>103</sup> which spent US\$1.5 million on research projects there from 1989 to 1996 (Table 3). The unit also received substantive funding from the North of England Cancer Research Campaign, the UK Medical Research Council (MRC) and the pharmaceutical company Bayer.

**Table 3: Tobacco-funded projects in the Pharmacogenetics Unit, University of Newcastle Upon Tyne**

Dates	Project	Funds	Funder	Researchers
1989-1990	A case/control study of breast and lung cancer with the addendum of the debrisoquine study*	US\$77,700 <sup>104,105</sup>	CTR	JR Idle
1989-1997	Cytochrome P450 polymorphisms	US\$772,000 <sup>106,107</sup> (£530,880 <sup>†</sup> )	BAT	JR Idle, AK Daly
1991-1994	Pharmacogenetic epidemiology of lung cancer	US\$296,500 <sup>108</sup>	CTR	JR Idle, AK Daly
1991-1994	Pharmacogenetics of nicotine metabolism	US\$318,700 <sup>109</sup>	STRC <sup>‡</sup>	JR Idle, S Cholerton

\* Idle’s collaboration with Professor Henry Lynch (Omaha, USA).<sup>110</sup> The first payment of US\$47,000 was made prior to Idle’s move to Newcastle and is not included in the table.

† Source: SRG budget documents. Two 3-year projects were funded.

‡ The Smokeless Tobacco Research Council (STRC), another tobacco-industry-funded body.<sup>111</sup>

BAT’s commitment to fund Idle’s project was made on 7 April 1988,<sup>112</sup> some days before his project was formally approved by the SRG<sup>113</sup> and several months before his research proposal<sup>114</sup> received an extremely critical review from Feinstein: a review which questioned his understanding of statistics.<sup>115</sup> The funding decision was influenced by a meeting with the leading molecular biologist (now a Nobel Laureate) Dr Sydney Brenner, then director of the MRC’s Laboratory of Molecular Biology (LMB) in Cambridge. BAT report that Brenner:

*“went so far as to recommend the industry should carry out screening, if appropriate, for those individuals carrying genetic markers for diseases such as lung cancer”.*<sup>116</sup>



The tobacco industry's main aim in funding projects like Idle's was to identify a "genetically susceptible" minority of smokers so that smoking cessation efforts could be targeted at them and "the rest of the population can be allowed to puff away contentedly and without serious risk".<sup>117</sup>

BAT met Brenner on 30 March 1988. By the end of April he was a founding member of the Human Genome Organisation (HUGO), an organization that he is credited with first proposing.<sup>118</sup> At the time, Brenner was also a member of the Council of the MRC.<sup>119</sup> According to the Wellcome Trust, it was Brenner who gained the personal support of the then prime minister, Margaret Thatcher, after Brenner and Sir Walter Bodmer (a former student of Ronald Fisher) initially had difficulty persuading influential bodies in the UK to 'think big' about the genome.<sup>120</sup> In 1986, Brenner had been told that any human genome mapping had to be undertaken within the MRC's existing budget, but after gaining the prime minister's support, the MRC was awarded an extra £11 million over three years, agreed in February 1989 and paid from the start of the 1989/90 financial year.<sup>121</sup> There is no suggestion that Brenner was receiving funding from the tobacco industry in March 1988. However, BAT's memo of the meeting notes that he "seemed quite willing to meet with BAT again on a specific subject".

A conference abstract by NIH researchers, sent "in confidence" by Idle to BAT, also appears to have influenced BAT's decision to fund his research.<sup>122,123</sup> The CTR's response to a 1989 *New York Times* article advocating genetic screening of smokers<sup>124</sup> was ecstatic, describing the NIH's statements as "vindication" of its research strategy,<sup>125</sup> and interest from the NIH prompted the CTR to invite Idle to resubmit one of his research proposals<sup>126</sup> and to make an extra payment to him.<sup>127,128</sup>

Beginning in 1988, a series of studies failed to confirm Idle's hypothesis of a link between CYP2D6 polymorphisms and lung cancer.<sup>129,130,131,132,133</sup> CTR-funded studies in Norway and Los Angeles also failed to confirm the association and both were ultimately published (in 1994 and in 1997). However, prior to the publication of the Los Angeles results, Idle co-authored a series of reviews<sup>134,135,136,137,138</sup> and conference papers<sup>139</sup> implying that genetic susceptibility to lung cancer had been firmly established.

One review was published in *Pharmacogenetics* when Idle was already aware that the preliminary results from Norway did not confirm the proposed association<sup>140</sup>. A response (also in *Pharmacogenetics*, but not published until two years later) concludes that the review is "factually misleading and gives an incorrect impression of ... the current conclusions which can be drawn from the literature".<sup>141</sup> Genetic variations in CYP2D6 are now thought to play little or no role in lung cancer.<sup>142,143,144,145</sup>

Henry Rothschild (University of Louisiana) was funded by the CTR from 1977.<sup>146,147</sup> In 1982, Rothschild gave evidence on behalf of the tobacco industry to the Waxman Hearings, which were considering proposals for new stronger warning labels on US cigarette packs. The industry argued that: "Science... would be frozen in its tracks if

Congress, through such legislation, tries to settle unresolved medical and scientific controversies.” Rothschild gave evidence that genetics may determine who gets lung cancer.<sup>148</sup> The following month, on the advice of tobacco-industry lawyers,<sup>149</sup> he was awarded a new ‘Special Project’ grant by the CTR to study genetic factors in lung cancer in Louisiana families.<sup>150</sup> Rothschild received US\$160,700 in total from the CTR for research on genetic factors in lung cancer.<sup>151,152,153,154</sup> He co-authored three papers during this time that claim to support the concept of genetic susceptibility to lung cancer (none acknowledge tobacco industry funding).<sup>155,156,157,158</sup>

In 1990 the *Journal of the National Cancer Institute (JNCI)* published two articles on genetic susceptibility to lung cancer – one by NCI researchers<sup>159</sup> and one by Sellers *et al.*,<sup>160</sup> on which Rothschild is a co-author and CTR funding is acknowledged. BAT describe the NCI researchers as “close to” Idle’s group.<sup>161</sup> The papers gained extensive press coverage,<sup>162,163,164</sup> some of which led to scientific criticism of the researchers for implying that genetics rather than smoking determines whether lung cancer develops.<sup>165</sup>

Following the publicity surrounding the Sellers *et al.* (1990) paper, this research group published two further related papers which acknowledge CTR funding<sup>166,167</sup> and three which do not.<sup>168,169,170</sup> Springall’s BAT-funded project sought to confirm the Sellers *et al.* findings, using the Louisiana data set (purchased by BAT for £25,000<sup>171</sup>). In 1993, Springall reported that he had successfully reproduced the segregation analysis<sup>172</sup>, following initial difficulties.<sup>173</sup>

Rothschild’s colleague J.E. Bailey-Wilson presented his team’s proposal for a pilot study of lung cancer probands with at least two affected relatives to BAT in October 1993<sup>174</sup>. The SRG minutes record that if the pilot study fails to identify any genetic markers, the team hopes to go on to a global screen of the genome, funded by the NIH. BAT subsequently agreed to fund Rothschild’s genetic-linkage project “pending funding by the NIH”.<sup>175</sup> We have been unable to identify any papers by Rothschild acknowledging BAT funding. Two NIH-funded papers by other authors also conclude that a major gene explains familial aggregation of lung cancer: both rely solely on Rothschild’s Louisiana data set.<sup>176,177</sup> In 2000, Rothschild was awarded three grants by the NIH, totalling more than US\$660,000, to continue his research.<sup>178</sup>

In 2004, Bailey-Wilson *et al.* published a paper identifying a major lung cancer susceptibility locus in 771 families with three or more first-degree relatives affected with lung cancer.<sup>179</sup> Press reports again claimed that the study paved the way for a genetic screening test to identify susceptible smokers.<sup>180,181,182</sup> The paper appears to report the next step in the pilot project presented to BAT by Bailey-Wilson in 1993, and subsequently funded via a grant to Rothschild “pending funding by the NIH”, as described above. Rothschild is a co-author on the paper. A subsequent paper, on which Bailey-Wilson and Rothschild are co-authors, investigates a different locus, again with funding from the NIH as part of the Genetic Epidemiology of Lung Cancer Consortium.<sup>183</sup> The paper claims that evidence of a genetic basis for susceptibility to lung cancer has been demonstrated through genome-wide association studies (citing three new studies<sup>184,185,186</sup>) and via the segregation analyses previously reported by

the group in Sellers *et al.* (1990) and subsequent papers. It reports a further genome-wide association study among individuals with a family history of lung cancer.

### *Genetic damage*

BAT supported a basic research programme on the p53 tumor suppressor gene at the Marie Curie Research Institute from 1987, led by its former director, Graham Currie. Currie's colleague John Jenkins also worked on the project, which received £240,000 over eight years to the end of 1993.<sup>187</sup> Bitton *et al.* (2005) document how this relationship gave BAT an early insight into research on p53, which they felt could lead to either benefits or problems for the industry.

One BAT-funded researcher, John Field, believed that research on p53 mutations had added weight to the link between smoking and lung cancer.<sup>188</sup> The original lead researcher on his project, Philip Stell, had given evidence on the tobacco industry's behalf in a smoking damages case in Finland in 1991<sup>189</sup> but Field took on the project when Stell retired. In March 1994, BAT decided that further funding for Field's project was "low priority"<sup>190</sup> and the SRG then noted: "Applications from other p53 researchers will be sought."<sup>191</sup>

In contrast, a discussion forum by Krawczek and Cooper,<sup>192</sup> published in *Mutagenesis* in 1998, uses an earlier paper, Krawczak *et al.* (1995)<sup>193</sup>, as the basis of a rebuttal of new evidence for a unique genetic fingerprint for tobacco smoke in p53 mutations in lung cancer cells. James Parry, editor in chief of *Mutagenesis* from 1986<sup>194</sup> until November 2001<sup>195</sup> was a BAT consultant in 1993<sup>196,197</sup> and in 1998 was receiving project funding from Philip Morris.<sup>198</sup> Bitton *et al.* (2005) note that no funding source or competing interests were reported in the discussion forum, but find no evidence that either Cooper or Krawczak received tobacco funding for this research. However, we have identified additional evidence that the earlier Krawczak *et al.* (1995) paper, on which the forum was based, was BAT-funded:

- Two of the authors (Cooper and Kakkar) received research funding from BAT (Kakkar from 1987-1992, for a project on arterial damage which we did not classify as 'genetic research' for the purposes of this investigation, see supplementary material S1; Cooper from 1992, as shown in Table 2).<sup>199</sup>
- A BAT note of a visit to Cooper in June 1992<sup>200</sup> and the minutes of two SRG meetings in 1993<sup>201,202</sup> outline the proposed comparison reported in the paper.
- A BAT note of a visit to Krawczak in Germany in September 1993 records that he is working with Cooper on a paper making this comparison and what they have found.<sup>203</sup>
- A BAT memo from July 1994 refers to an enclosed "paper in press" from Cooper and cites part of the abstract.<sup>204</sup>
- A BAT memo from March 1995 outlines new evidence linking mutations in the p53 gene to tobacco smoke and references Krawczak *et al.* (1995) as the basis of BAT's rebuttal of the evidence.<sup>205</sup>

Bitton *et al.* (2005) document how Parry again published a response in *Mutagenesis* when further evidence that smoking causes specific mutations to the p53 gene was

published, this time from an author based at a private institute sponsored by the German Association of Cigarette Manufacturers. When one of the authors of the original paper discovered Parry's tobacco industry links, the journal's publishers introduced a conflict of interest policy. Parry, who did not sign up to the arrangement, then left his role as Editor-in-Chief, and transferred to a non-executive role on the editorial board.<sup>206</sup>

Poulsen, Clausen and Farmer's projects investigated different types of DNA damage (oxidative damage and DNA adducts) in smokers and non-smokers. Poulsen's research included attempts to try to reduce oxidative DNA damage in smokers by giving them dietary supplements.<sup>207</sup> The efficacy of this approach is questionable<sup>208</sup> and beta-carotene supplements are now believed to increase risk of death in smokers.<sup>209,210,211</sup>

### *Other issues*

We did not analyse the documents we collected which relate to environmental tobacco smoke (ETS). However, we found one example where genetic research was used to seek to undermine evidence of children's exposure to ETS. In 1990 BAT's consultant Feinstein published a commentary by Idle in the *Journal of Clinical Epidemiology* criticising work on ETS by Jarvis *et al.*<sup>212,213</sup> In the article, which did not declare tobacco funding, Idle argued that genetic variations in cotinine metabolism make cotinine tests an unreliable measure of tobacco smoke exposure. Philip Morris had commissioned an outline of a review of cotinine from Idle in March 1989.<sup>214,215</sup> A faxed copy of his paper is in Philip Morris' files, dated 4 July 1989,<sup>216</sup> a week before the *Journal of Clinical Epidemiology* recorded receiving it. Idle copied his acceptance letter from Feinstein to BAT, saying:

*"Dear Ray, with the compliments of Professor Jeffrey Idle, Cotinine editorial now in press! (no changes asked for!) Regards Jeff."*<sup>217,218</sup>

### **Discussion**

Our research has some limitations. We focused on the academic research funded by a single company (BAT) and restricted our analysis to projects involving human genetics. Our searches and the documents themselves may not be comprehensive, nor are recent documents generally available. However, our approach also has some strengths. Firstly, the SRG budgets we obtained are complete for the period 1990-1995, enabling us to assess the relative importance of the different projects at this time. Secondly, searching the CTR and Philip Morris collections and PubMed for the names of the BAT consultants and researchers allowed us to build an in-depth picture of the history of the projects and related journal publications. Searching by name is one of the most effective strategies for identifying tobacco industry documents.

The majority of SRG-funding in the period 1990-1995 was spent on human genetic research. The main area of research was genetic predisposition to lung cancer. Research was also used to counter potential threats to business (particularly the link between p53 mutation patterns and tobacco smoke) and to study ineffective alternatives to tobacco control (such as giving smokers vitamin supplements).

The tobacco industry selected research projects to suit its own strategic interests. Lawyers and public relations firms both played a role in influencing its research agenda. The industry's influence did not lie in scientific fraud or suppression of results, but in providing significant support for those researchers who adopted its perspective. Idle, for example, remained sceptical that smoking causes lung cancer until at least 1999, when he endorsed Fisher's theory in a letter to the *Lancet*.<sup>219</sup> Vijay Kakkar, director of the Thrombosis Research Institute in London, where Cooper was based, reportedly informed the SRG in June 1992 that his hypothesis was that the most important risk factor for heart disease is not smoking, but levels of mercury in water. In addition, journal editors who were also receiving industry funding as consultants 'placed' editorials from seemingly independent scientists to support the industry's position in matters of scientific controversy.

The tobacco industry's funding decisions played an important role in shaping the genetic research agenda, contributing to a scientific "race to find the gene or genes which predispose to lung cancer".<sup>220</sup> Idle, in particular, boasted of his connections with the NIH and was a member of the Lung Cancer Task Force at the US National Cancer Institute (NCI) from 1984, when the NIH began to increase massively its spending on cancer genetics research, creating the "scientific bandwagon" described by Fujimura (1988).

Our research suggests that a coincidence of interests between advocates of molecular genetic research and the tobacco industry helped to drive this scientific bandwagon, as demonstrated by the timing of the meeting between BAT and Sydney Brenner. This meeting led to the establishment of Idle's pharmacogenetics unit in 1988 - with funding from the tobacco industry, Bayer and the MRC - at a time when Brenner was anxious to convince the Thatcher government of the industrial applicability of human genome mapping. Brenner was not receiving funding from BAT at the time of the reported meeting. However, some years later, in 1996, the journal *Science* reported that a new 'Molecular Sciences Institute', based at La Jolla in the USA, for which Brenner had been recruited as director, was to receive a grant of \$15 million a year for 15 years from Philip Morris (a plan which appears to have been first discussed with Brenner in 1994<sup>221</sup>).<sup>222</sup> Following this exposé, Brenner and Philip Morris terminated their research funding agreement for the institute.<sup>223</sup>

The benefits to the tobacco industry of the promotion of gene screening for smokers are clear: it regarded the public endorsement of genetic screening by the NCI in press stories in 1987 and 1990 as "favorable publicity" and "vindication" of the research strategy that it had followed since the 1950s. Media stories about genetics are likely to exert a powerful public influence<sup>224</sup> and self-exempting beliefs, such as believing in genetic causes for lung cancer, are one strategy used by smokers to avoid facing the difficulties involved in quitting smoking.<sup>225</sup> Combined with the Thatcher government's reluctance to strengthen tobacco control measures, it seems likely that the promotion of this 'scientific solution' to the problem of lung cancer both benefited the industry and harmed public health.



The main advantages for the scientific proponents of molecular genetics were: the opportunity to claim that their research could have a major impact on the incidence of cancer, rather than being restricted to studying biological mechanisms and rare familial diseases; and the chance to gain support from industry. This was particularly important as they sought to win public and political support (including financing) for human genome mapping in both the UK and the USA (where the Human Genome Initiative was launched in 1991).

The difficulties in replicating genetic association studies are now well known<sup>226</sup> and we found no evidence of scientific fraud. However, we did find evidence of interpretative bias (particularly “rescue bias”<sup>227</sup>) as contradictory evidence was discounted or ignored. Early studies tended to over-estimate genetic risk and in some cases expression of the relevant enzyme in the lung is very low<sup>228,229</sup> or non-existent,<sup>230</sup> making a role in lung cancer unlikely. In the case of Idle’s research, this situation was exacerbated by ‘self-publication’ in a journal which he edited and founded, and his poor grasp of statistical method.

Rothschild’s group also drew erroneous conclusions, probably as a result of sloppy science, rather than an intention to mislead. Familial aggregation of disease does not necessarily imply a genetic component<sup>231</sup> and segregation analysis is sensitive to the assumptions made, which may give rise to spurious evidence of Mendelian inheritance.<sup>232</sup>

In general, researchers seem to have genuinely believed that they could benefit their own careers and at the same time find a ‘scientific solution’ to the lung cancer problem that would also benefit the industry. Thus Proctor (1995) reports that molecular epidemiologists were surprised when a 1994 NIH twin study found “little if any effect of inherited predisposition on development of lung cancer”. Earlier twin studies had also failed to identify an inherited component, but, in the excitement of the race to find the genes for lung cancer, it had simply been presumed that these studies were not large enough. Small differences in genetic risk could still exist, as could rare cases of familial lung cancer, but this does not mean that genetic screening can be used to ‘predict and prevent’ lung cancer in the general population.<sup>233,24</sup>

The idea that genetic screening would be of benefit to smokers nevertheless persists in the scientific literature and in the media. In 2003, press reports based on a new scientific paper<sup>234,235</sup> claimed that a genetic test would be developed within three to four years to “show which smokers face lung cancer death”.<sup>236,237,238,239,240</sup> Searches we conducted using the CTR website revealed that the study’s corresponding author and press spokesman, Professor Zvi Livneh, had a history of funding from the tobacco industry (receiving \$519,069 in funding from the CTR from July 1985 to June 1992)<sup>241,242,243,244,245,246,247</sup>.

Although genetic population screening has not (yet) been implemented, the policy implications of our findings are significant. In 1995, Idle co-authored a paper in *Pharmacogenetics* which advocates genetic screening of whole populations, with data stored on individual patient SMART cards, and expert computer systems on every



doctor's desk.<sup>248</sup> This idea, and claims that this approach would be of benefit to public health, subsequently became widely advocated: most famously in a May 1999 lecture given by the leader of the Human Genome Project at the NIH, Francis Collins,<sup>249</sup> by the UK Prime Minister Tony Blair in 2002,<sup>250</sup> and in a 2003 UK Government White Paper which set out a vision for genetics in the National Health Service.<sup>251</sup> Yet, 20 years after BAT helped to establish the first university pharmacogenetics unit, there is still limited potential for the genetic variants thus far identified (singly or in combination) to provide clinically useful prediction of either common diseases (including cancer) or adverse drug reactions in the general population.<sup>252, 253, 254, 255, 256</sup>

Our findings highlight the need for policy-makers, academic institutions and charities to take greater care to avoid conflicts of interest and to set health research priorities that are in the public interest, not in the interests of tobacco companies. More broadly, other industries – including the food and pharmaceutical industries – may have vested interests in promoting human genome screening, as may governments who are interested in expanding DNA databases for surveillance purposes.<sup>257, 258</sup>

Our research suggests that the main danger lies in failure to scrutinise the exaggerated promises that scientists make to both policy makers and the media in order to secure funding, rather than in scientific fraud.<sup>259, 260, 261</sup> As Rose (1994) describes, fear of cancer became a powerful motivator for science funding for the Human Genome Project, but this also involved a political commitment to looking for causes *within* the human body (to the supposedly determining genetic code), rather than *outside*, at the causes to be found within everyday life and people's environments.<sup>262</sup> The opportunity costs may be significant. Nightingale and Martin (2004) state:

*“Unrealistic expectations are dangerous as they lead to poor investment decisions, misplaced hope, and distorted priorities, and can distract us from acting on the knowledge we already have about the prevention of illness and disease”.*<sup>263</sup>

We conclude that the tobacco industry has played a significant role in shaping research agendas: in particular, by promoting the idea that individual genome screening would be of benefit to public health. Commercial vested interests can create and drive scientific bandwagons by bankrolling research in scientific institutions, and placing reviews and articles in scientific journals, thus attracting public funding and building political support. This may drain considerable resources from more valuable approaches, wasting time and money and ultimately costing lives.

Our research suggests that transparency, whilst undoubtedly important, is not enough to ensure that science is conducted in the public interest. Many of Idle's papers, for example, did declare his funding sources, apparently without limiting the tobacco industry's influence on the research agenda or reporting of that research, both in scientific journals and in the wider press. It seems likely that subsequent decisions by many funders, including the MRC, NIH and most major charities, to cease co-funding tobacco industry research has been more effective. From 1988-1994 only one UK

medical school did not accept tobacco funding,<sup>264</sup> and charities that jointly funded the research described above included: the Wellcome Trust,<sup>53,59</sup> the North of England Cancer Research Campaign and the North of England Childrens' Cancer Research Campaign, the American Cancer Society, the Norwegian Cancer Society and Stop Cancer (California).<sup>80,81,82</sup> However, the decision to cease co-funding has not prevented other industries from adopting similar approaches.<sup>265</sup>

Our findings highlight how research funding mechanisms established by the Thatcher and Reagan governments allowed vested interests to set research priorities in universities and public institutions and to encourage widespread publication, endorsement and reporting of spurious scientific findings. We recommend that, in addition to transparency, more democratic decisions about research funding priorities are required. This should include greater public accountability and scrutiny of research investment decisions, and active steps to prevent political 'entrapment' in research agendas based on false assumptions and misleading claims.

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**S1: SRG Research Projects, 1990-1995**<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16</sup>

Lead Researcher	Institution	Project	Funding (*)
Professor JR Idle	Department of Pharmacological Sciences, University of Newcastle Upon Tyne, UK	Cytochrome P450 polymorphisms	1989: £56k 1990: £72k 1991: £85.1k 1992: £88.7k 1993: £96k
Dr AK Daly	Pharmacogenetics Research Unit, University of Newcastle Upon Tyne, UK	Cytochrome P450 polymorphisms	1994: £43k 1995: £44.4k 1996: £45.6k
Dr ND Carter	St George's Hospital Medical School, Department of Child Health, London, UK	Identification of DNA polymorphisms in a hypertensive and control population from South London	1987: £26.5k 1988: As '87 plus inflation 1989: As '87 plus inflation 1990: £36.5k
Professor I Hindmarch	Human Psychopharmacology Research Unit, University of Leeds, UK	Human psychopharmacology of nicotine	1988: £56k 1989: As '88 plus inflation 1990: £61.6k 1991: £15k
Professor JR Clamp	University of Bristol, Department of Medicine, Bristol Royal Infirmary, UK	Effect of smoking on mucosal protection in the colon	1987: £15.5k 1988: As '87 plus inflation 1989: As '87 plus inflation
Newsom-Davis			1991: £14.3k
Professor J Clausen	Roskilde University, Denmark	DNA adducts	1990: £22k 1991: £11.7k 1992: £55.9k 1993: £34k
Dr VJ Knott	Royal Ottawa Hospital, Canada	Nicotine and brain activity	1990: £68.2k 1991: NIL 1992: £49.2k 1993: £54k
Dr G Currie	Marie Curie Research Institute, Oxted, Surrey, UK	p53 and cell cycle	1990: £31.9k 1991: £34.8k 1992: £35k 1993: £40k
Dr T Jelsma	Marie Curie Institute, UK	p53 and cell cycle	1989: £28.8k
Professor PM Stell	Department of Otorhinolaryngology Royal Liverpool Hospital	p53 in head and neck cancer	1991: £15.2k
Dr JK Field	Department of Clinical	p53 in head and neck	1992 <sup>17</sup> : £32.5k

	Dental Sciences, School of Dentistry, University of Liverpool	cancer (taken over from Stell)	1993: £32.5k
Professor VV Kakkar	Thrombosis Research Institute, King's College School of Medicine, London, UK	Antifunctional and other reagents against platelet-derived growth factor	1987: £31.6k 1988: As '87 plus inflation. 1989: As '87 plus inflation 1990: £35.2k 1991: £34.8k
Dr DN Cooper	Thrombosis Research Institute, London	Mutations in thrombotic disease	1992: £24.7k 1993: £42.5k 1994: £65k 1995: £22.5k
		Unstable trinucleotide repeats/ Factor VII	1996: £44.4k 1997: £48k
Professor K Syrjanen	University of Kuopio, Finland	Human papillomavirus	1992: £42.6k 1993: £43k 1994: £59.4k
Dr A Springall	Clevedon, UK	Segregation analysis	1991: £12.7k 1992: £30k 1993: £30k
Mr PN Lee	PN Lee Statistics and Computing Ltd, Sutton, Surrey, UK	Lifestyle confounders of ETS exposure	1992: £31k 1993: £35k 1994: £42k 1995: £25k
		Hungarian Lifestyle Project	1994: £30k 1995: £76.4k 1996: £20k
Professor MA Smith	Leeds General Infirmary, UK	Osteoporosis	1992: £20k 1993: £24k 1994: 22.8k 1995: £11k
Dr P Farmer	MRC Toxicology Unit, Leicester, UK	DNA adducts and free radical damage	1993: £20k 1994: £20k 1995: £20k 1996: £20k
Professor J Gray	Institute of Psychiatry, London, UK	Effects of nicotine on attention in Alzheimers	1987: £29.5k 1988: As '87 plus inflation 1989: As '87 plus inflation 1990: £9.3k
		Nicotine, reinforcement and cognition	1991: £37.2k 1992: £40.9k 1993: £44k
		Neuro-degenerative disease	1993: £37.5k 1994: £75k 1995: £40k
Professor H Poulsen	University of Copenhagen, Denmark	Oxidative DNA damage	1994: £85k 1995: £60k 1996: £60k

Dr H Rothschild	Louisiana State University Medical Centre, New Orleans, USA	Human genetics of lung cancer	1994: £42k 1995: £38k 1996: £38k
Professor D Barker	MRC Environmental Epidemiology Unit, Southampton, UK	Foetal Nutrition and Disease	1994: £30k 1995: £30k 1996: £30k
Dr E Perry	MRC Neurochemical Pathology Unit, Newcastle Upon Tyne, UK	Effects of chronic nicotine in human brain	1995: £49k 1996: £49k 1997: £49k
Dr S Wonnacott	University of Bath, UK	Nicotinic acetylcholine receptor plasticity	1995: £51k <sup>18</sup>
Nelson		Review of cytokines	1995: £11k

(\*) Figures for 1995-1997 are BAT projections based on money committed.

Additional proposals/areas under consideration for 1996/97 but not yet confirmed were: Wonnacott's "Nicotine acetylcholine receptor plasticity" (£51k proposed for 1996); Feinstein's "Epidemiology of smoking-related diseases" (£40k proposed for 1997); Salonen's "Antioxidant supplementation in atherosclerosis prevention" (£40k proposed for 1996 and £40k for 1997); Kakkar's "Epidemiological study of heart disease in India" (£30k proposed for 1996 and £30k for 1997), Nelson's "Cytokines and lung disease" (£40k proposed for 1997), Holgate's "Asthma" (40k proposed for 1997) and Farmer's "Oxidative damage" (£30k proposed for 1997).

The BAT projects incorporated into the SRG research budget from 1993 were those by Springall, Lee, Smith and Syrjanen<sup>19</sup>.

<sup>1</sup> Anon (undated), Research & Development: List of Smoking and Health Contracts. Bates No. 500874413-4415. L. Waters, (undated), Details of SRG Contracts. Bates No. 500874416-4419. Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_ctr1.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_ctr1.pdf). Accessed: 31 August, 2008.

<sup>2</sup> BAT (undated). Bates No. 500874431. Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/idle\\_salary.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/idle_salary.pdf). Accessed: 31 October, 2008.

<sup>3</sup> R.E. Thornton, Scientific Research Group Budget 1990-1991, 27 September 1990. Bates No. 300524524. Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_bud\\_9091.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_bud_9091.pdf). Accessed: 31 August, 2008.

<sup>4</sup> R.E. Thornton, Note to Members of the SRG: SRG Budget 1990/1991, 4 December, 1990. Bates No. 400313790. Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_9091\\_bud.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_9091_bud.pdf). Accessed: 31 October, 2008.

<sup>5</sup> SRG, SRG Budget 1991 onwards. Bates No. 510100061. Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_91budget.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_91budget.pdf). Accessed: 31 October, 2008.

<sup>6</sup> Anon (undated), SRG Budget 1992. Bates No. 510100033. Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_budget92.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_budget92.pdf). Accessed: 31 October, 2008.

<sup>7</sup> Anon (undated), SRG Budget 1992; BATCO Smoking and Health Budget 1992. Bates No. 300528514-8515. Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_92\\_bud.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_92_bud.pdf). Accessed: 31 October, 2008.

<sup>8</sup> Anon (undated), SRG Budget 1991/1992. Bates No. 300524700. Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_bud\\_9192.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_bud_9192.pdf). Accessed: 31 October, 2008.

<sup>9</sup> BAT, Fax from L Rudge to G.A. Read, SRG Costings, 4 January 1993. Bates No. 400501207-1210. Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_bud\\_9293.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_bud_9293.pdf). Accessed: 31 October, 2008.

<sup>10</sup> Anon (undated), Projects - 1993 SRG Work Programme; BATCo Smoking and Health Budget

Projects 1992. Bates No. 300528449-8450. Available from:

[http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_93\\_work\\_prog.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_93_work_prog.pdf). Accessed: 31 October, 2008.

<sup>11</sup> Anon (undated), Projected SRG Budget for 1993. Bates No. 510100034. Available from:

[http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_budget93.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_budget93.pdf). Accessed: 31 October, 2008.

<sup>12</sup> SRG, Minutes of the SRG Meeting New York US, 28-30 October, 1993 (first page only – see ref 25 for full minutes). Bates No. 500834102. Anon (undated), SRG Budget 1994. Bates No. 500834110.

Available from: [http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_bud\\_9394.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_bud_9394.pdf).

Accessed: 31 October, 2008.

<sup>13</sup> BAT, Memo from L. Rudge to C.J.P. de Siqueira *et al.* Encl. Proposed SRG Budget 1994, 21 December 1993. Bates No. 400500861-0862. Available from:

[http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_94\\_ctrs.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_94_ctrs.pdf). Accessed: 31 October, 2008.

<sup>14</sup> Anon (undated), 1994/1995 SRG Budget. Bates No. 403692487. Available from:

[http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_bud\\_9495.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_bud_9495.pdf). Accessed: 31 October, 2008.

<sup>15</sup> BAT, Memo from L. Rudge to SRG Members, 15 February 1995. Bates No. 500833937. Summary of Research Projects Funded by the SRG in 1995. Bates No. 500833942-3947. Available from:

[http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_95\\_bud.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_95_bud.pdf). Accessed: 31 October, 2008.

<sup>16</sup> Anon (undated), Current Projects (Money Committed)/ Proposals (Areas for Consideration). Bates No. 500834080-4081. Available from:

[http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_95\\_bud.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_95_bud.pdf). Accessed: 31 October, 2008.

<sup>17</sup> The budgets for this project appear to be incomplete, presumably due to Stell's sudden resignation at the end of 1991. However a total of £65,000 over two years is recorded as having been paid to Field's project to end 1993, with work actually continuing until April 1994. R.E. Thornton, Note for the Tobacco Strategy Group, 2 December 1993. Bates No. 502520669-0672. Available from:

[http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_93.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_93.pdf) Accessed: 31 October, 2008.

<sup>18</sup> BAT states "Paid in '94" but no figure is given. However the total is recorded in S. Wonnacott, (undated), Current Grant Support. Bates No. 50650961-0961. Available from:

<http://legacy.library.ucsf.edu/tid/try36d00/pdf>. Accessed: 31 October, 2008. (Wonnacott applies to the CTR for funds to supplement the project but her application is rejected.)

<sup>19</sup> L. Rudge, SRG Budget 1993. 20 January 1993. Available from:

[http://old.ash.org.uk/html/conduct/pdfs/genetics/srg\\_cost\\_93.pdf](http://old.ash.org.uk/html/conduct/pdfs/genetics/srg_cost_93.pdf). Accessed: 31 October, 2008.



**S2: Idle chronology**

Date	Development
17 Sep 1977	Idle (at St Mary's Hospital) co-authors paper on role of CYP2D6 in debrisoquine metabolism. <sup>1</sup>
Jul 1980	Idle co-authors abstract suggesting CYP2D6 is linked to the risk of lung cancer in smokers. <sup>2</sup>
Feb 1981	Idle co-authors paper on debrisoquine metabolism in Nigerian cancer patients. <sup>3</sup>
11 Jun 1981	Notes from a talk by Idle in CTR files. <sup>4,5</sup> (The talk is published in 1982. <sup>6</sup> )
8 Nov 1984	Idle co-authors Nature paper on genetic susceptibility to lung cancer. <sup>7</sup>
1984	Idle joins Lung Cancer Task Force at the US National Cancer Institute (NCI). <sup>8</sup>
1986-91 (and 1995-98)	Idle joins Cancer Research Advancement Board at the Irish Cancer Society. <sup>8</sup>
1 July 1986	Idle joins the CTR's Scientific Advisory Board (SAB). <sup>9</sup> He informs CTR in his CV that his 1984 Nature paper "may herald a long-overdue change in the practice of epidemiology" and that he has established collaboration with the NIH to pursue "the host factors which determine individual lung cancer risk."
3 Mar 1987	Idle presentation on nicotine metabolism to the SAB. <sup>10</sup>
21 May 1987	" <i>Genetics linked to lung cancer predisposition</i> " press story, with Idle's work endorsed by the NCI and by Dr Alfred Knudson (another SAB member). <sup>11</sup>
18 Jun 1987	The CTR board discuss the "recent favorable publicity" relating to Idle and Knudson's work. <sup>12</sup>
11 Dec 1987	Idle presents his research at the CTR annual meeting. <sup>13</sup>
Dec 1987	CTR approve a \$47k grant to Prof Henry Lynch to collaborate with Idle <sup>14</sup> , as part of Lynch's existing project. <sup>15,16,17</sup>
Dec 1987	Idle writes a research proposal for the "Establishment of a Laboratory of Cancer Pharmacogenetics".
Jan 1988	The CTR's PR consultant sends Idle's laboratory proposal to BAT's PR consultant, asking for the names of UK companies that might back the plan. <sup>18</sup>
5 Feb 1988	Idle interviewed by BBC about genetic susceptibility to cancer. <sup>19</sup>
24 Feb 1988	SRG Chair informs BAT's Chairman (Patrick Sheehy) that Idle "is Professor elect at a greatly extended and revamped department of Pharmacology at Newcastle University (where BAT also has connections) and I anticipate that through the Scientific Research Group we shall be supporting his work there". <sup>20</sup>
18 Mar 1988	Idle sends a copy of an NIH abstract on genetic susceptibility to lung cancer " <i>in confidence</i> " to BAT. <sup>21,22</sup>
30 Mar 1988	BAT meet the molecular biologist Dr Sydney Brenner, who supports the idea of genetic screening for lung cancer susceptibility. <sup>23</sup>
7 Apr 1988	BAT write to Idle confirming they will fund his project (referring to a proposal made on 28 March). <sup>24</sup>
18-20 Apr 1988	The SRG meeting agrees to fund Idle. <sup>25</sup>
21 Apr 1988	BAT's consultant Roe comments on Idle's proposal <sup>26</sup> including a note on the historical background to tobacco industry's interest in genetic susceptibility.
1 Jun 1988	A lunch appointment is made for Idle to meet Sheehy on 25 July. <sup>27</sup>
23 Jun 1988	Idle is a guest in the BAT tent at Wimbledon. <sup>28</sup> Other guests include Sir Peter Froggatt, chair of the Independent Scientific Committee on Smoking and Health.
2 Sep 1988	Idle's research proposal to the SRG: "Molecular Epidemiology of Lung Cancer Risk". <sup>29</sup>

29 Sep 1988	BAT send a five year “research agreement” to the University of Newcastle. <sup>30</sup>
Oct 1988	Idle becomes Professor of Pharmacogenetics at the University of Newcastle Upon Tyne, UK. <sup>31</sup>
19 Dec 1988	Feinstein’s review of Idle’s BAT proposal severely criticises his epidemiology. <sup>32</sup>
1988	Paper by Roots <i>et al.</i> suggests Idle’s proposed association (between debrisoquine metabolism and lung cancer) is either weak or does not exist. <sup>33</sup>
1989	Idle is WHO Committee Chairman “Genetic predisposition to toxic effects of chemicals”.
1 Jan 1989	BAT begins funding Idle’s project. <sup>34</sup>
27 Mar 1989	CTR visits Lynch and express doubts about Idle’s part of his project. <sup>35</sup>
Mar 1989	Daly joins Idle at Newcastle. <sup>36</sup>
Mar/Apr 1989	Idle paper reviewing his previous work on lung cancer susceptibility. <sup>37</sup>
3 May 1989	Glenn (CTR Scientific Director) informs Idle they cannot fund him outside the normal grant process. <sup>38</sup>
May 1989	Idle co-authors a paper linking genetic predisposition to lung cancer to debrisoquine metabolism <sup>39</sup> . Idle had sent the final manuscript to BAT in January with a note: “...Nowhere does it say that smoking causes lung cancer...” <sup>40</sup>
16 May 1989	<i>New York Times</i> article <sup>41</sup> predicting that genetic tests for vulnerability to cancer will be available in 3 to 5 years. Quotes NCI researchers saying that genetic tests could help focus anti-smoking efforts.
June 1989	“VINDICATION” speech by a CTR employee, about the <i>New York Times</i> article and the views expressed by NCI <sup>42</sup> . Refers to Idle as one CTR researcher working on genetics and lung cancer.
1 July 1989	Idle and NCI researchers publish a paper on susceptibility to lung cancer in workers exposed to occupational carcinogens, which advocates screening and targeting of susceptible individuals. <sup>43</sup>
Jul/Aug 1989	Idle and NCI researchers publish a paper re-analysing the data from 1984 <i>Nature</i> paper and supporting its conclusions. <sup>44</sup>
2 Aug 1989	CTR staff meeting notes that NCI “has indicated interest” in Idle’s research and that they have asked Idle to resubmit his application. <sup>45</sup>
4 Oct 1989	Lynch requests \$24,500 to extend Idle’s part of his CTR project (this is approved). <sup>46</sup>
31 Oct 1989	<i>Wall Street Journal</i> article, quoting NCI advocating genetic testing for lung cancer. <sup>47</sup>
4 Nov 1989	Idle publishes a <i>Lancet</i> commentary advocating his theory. <sup>48</sup>
30 Nov 1989	Idle applies for a CTR grant. <sup>49,50</sup> The proposal refers to an attached letter of collaboration from NCI.
20 Dec 1989	Idle informs CTR that he has received a letter of collaboration from NCI and seeks an additional \$20,000 for his research with Lynch. <sup>51</sup>
4 Jan 1990	CTR agrees to pay the \$20,000 requested by Idle. <sup>52</sup>
5 Jan 1990	Idle writes to Glenn to thank him <sup>53</sup> : “We may now be on the road to lay some myths to rest!”
March 1990	Idle’s CTR proposal receives mixed reviews. <sup>54,55,56,57</sup>
17-20 April 1990	Idle’s CTR proposal is withdrawn (no reasons given).
July 1990	Idle and his NCI co-author publish a paper defending the conclusions of their studies <sup>58</sup> against new data that does not support their findings <sup>59,60</sup> . No funding acknowledgements.
10 July 1990	Letter from Idle explaining that his chapter is missing from a recent WHO publication because the WHO objected to his view that there is “an uncomfortable credibility gap in the widely-held belief that cigarettes cause lung cancer...” <sup>61</sup> (Note: an unedited draft of this paper is in Philip Morris’ files, 21 Sep 1989). <sup>62</sup>
17 July 1990	SRG visit Idle at Newcastle. <sup>63</sup>
1 Aug 1990	The <i>Journal of the National Cancer Institute</i> (JNCI) publishes two articles on genetic susceptibility to lung cancer – one by NCI researchers <sup>64</sup> and one by Sellers et al (who

	acknowledge CTR funding). <sup>65</sup> The editorial <sup>66</sup> suggests that the two papers may have identified the effect of the same gene. BAT describe the NCI group as “close to” Idle’s group. <sup>67</sup>
August 1990	The JNCI papers gain extensive press coverage. <sup>68,69,70</sup>
6 Oct 1990	Letter from Idle and colleagues to the <i>Lancet</i> about developing tests of variations in the CYP2D6 gene <sup>71</sup> . No tobacco industry funding is acknowledged.
15 Oct 1990	Letter to Idle from Stephanie London (University of California School of Medicine) agreeing to collaborate and send DNA samples. <sup>72</sup>
18 Oct 1990	Idle writes to CTR seeking an additional £29,500 (\$57,741) to begin work with London. <sup>73</sup>
30 Oct 1990	CTR approves a supplemental grant of \$57,741 to Idle via Lynch. <sup>74</sup>
26 Nov 1990	Idle and Daly re-apply for a CTR research grant to include collaborations with London in Los Angeles and Dr Anne-Lise Børresen in Norway. <sup>75</sup>
Jan 1991	The authors of the 1990 JNCI papers are criticised for implying that genetics rather than smoking determines when lung cancer develops. <sup>76</sup>
4 Mar 1991	Idle and Daly’s progress report to BAT, <sup>77</sup> enclosing a paper submitted to Molecular Pharmacology.
Apr 1991	Idle publishes a review of genetic susceptibility to cancer which criticises IARC for emphasising the role of tobacco in lung cancer and omitting the genetic constitution of the population <sup>78</sup> . No acknowledgement of tobacco-industry funding.
Apr 1991	Idle and Daly’s project “Pharmacogenetic Epidemiology of Lung Cancer” is considered at the CTR’s SAB meeting and funded as requested. <sup>79</sup>
1 Jul 1991	Idle and Daly’s CTR project begins. They receive \$96,538 in year 1, \$100,000 in year 2 and \$99,959 in year 3. <sup>80</sup>
8 Aug 1991	Letter from Daly to BAT seeking travel funds and saying the manuscript sent to them in March will now be published in the new journal <i>Pharmacogenetics</i> . <sup>81</sup>
Oct 1991	The first edition of <i>Pharmacogenetics</i> is published. Idle is a founding editor and Editor-in-Chief (until October 1998) <sup>82,83</sup> . It includes the Daly <i>et al.</i> paper, <sup>84</sup> which acknowledges part funding from BAT.
15 Oct 1991	Idle resigns from the CTR’s SAB following a dispute about expenses. <sup>85,86</sup> He continues to receive project funding. <sup>87</sup>
Nov 1991	Idle co-authors a paper in <i>Pharmacogenetics</i> , finding a low frequency of ‘poor metabolisers’ in Turkey. <sup>88</sup> No funding acknowledgements.
4 Dec 1991	Idle and Daly’s renewal application for the second year of their CTR grant. <sup>89</sup> Informs the CTR that their Norway study does not support Idle’s earlier findings.
1991	Two further papers cast doubt on Idle’s findings. <sup>90,91</sup>
1992	Daly and Idle’s progress report to BAT for 1991. <sup>92</sup>
25 April 1992	Idle and Daly co-author a paper on genetic variations in CYP2D6 in patients with Parkinson’s disease. <sup>93</sup> Acknowledges part funding from BAT.
5-7 May 1992	BAT’s SRG minutes note the large number and complexity of metabolising enzymes and state: “it appears unlikely that a specific relative risk for individuals can be calculated”. <sup>94</sup>
30 Nov 1992	Idle and Daly’s renewal application for the third year of their CTR grant <sup>95</sup> . Reports that the Norwegian part of their study has found no link between CYP2D6 polymorphisms and lung cancer, but argues there may have been recruitment problems which will not arise in the larger Los Angeles study.
Nov 1992	New results from NCI researchers report only a weak association between CYP2D6 and lung cancer. <sup>96</sup>
Dec 1992	Idle and 18 of his Newcastle colleagues publish a review of genetic susceptibilities to cancer in <i>Pharmacogenetics</i> . <sup>97</sup> They criticise a recent study (Wolf <i>et al.</i> , 1992 <sup>98</sup> ) that found no link between CYP2D6 and lung cancer risk. Funding acknowledgements include BAT, the CTR and the STRC.
1993	Idle becomes Chief Executive of Genotype Ltd <sup>99</sup> as well as head of department and head of the School of Clinical Medical Science at Newcastle. He has raised £2 million in outside funding for the Pharmacogenetics Unit since 1988.

Feb/ Mar 1993	Daly, Idle and review genetic variations in metabolism, claiming that the majority of studies are confirming Idle's findings. <sup>100</sup> Funding from BAT, the CTR and the STRC is acknowledged.
7-9 Jun 1993	The SRG reports that Idle and Daly are awaiting the results of the LA study; developing genetic tests for GSTM1 and CYP2E1 and have made a new research proposal. <sup>101</sup>
Jul 1993	Daly and Idle co-author a short paper identifying another genetic variation in CYP2D6 <sup>102</sup> . BAT and CTR funding is acknowledged.
Aug 1993	Daly and Idle co-author a paper on the GSTM1 gene and bladder cancer. <sup>103</sup> Funding from BAT and the CTR is acknowledged.
Aug 1993	Idle and Daly's revised application to BAT <sup>104</sup> (includes CYP1A2, CYP2A6, CYP2D6, CYP2E1). Visit from SRG Chair (Thornton) to Idle and Daly. <sup>105</sup>
Oct 1993	Idle, Daly and Newcastle co-workers publish a review of genetic susceptibility to cancer, stating CYP2D6, CYP1A1 and GSTM1 are recognised candidate genes and that data are beginning to emerge on CYP1A2 and CYP2E1 <sup>106</sup> . Acknowledges BAT and CTR.
20 Oct 1993	BAT agrees to fund the "Interindividual variation in nitrosamine metabolism" project, with Daly as lead investigator, from 1 January 1994 to 31 December 1996. <sup>107</sup>
28-30 Oct 1993	SRG meeting. <sup>108</sup> Notes that trying to identify whether some smokers who develop lung cancer are "genetically susceptible" is one of the original aims of tobacco industry research and is still being supported.
30 Nov 1993	Idle and Daly apply to CTR for a further three years' of funding <sup>109,110</sup> , enclosing two letters of collaboration. <sup>111,112</sup>
Jan 1994	Idle co-authors another review of genetic variations and drug metabolism, which also states that CYP2D6 has been shown to be associated with cancer risk. <sup>113</sup>
1 Jan 1994	Idle co-authors a letter to the <i>Lancet</i> on the link between genetic variations in CYP2D6 and nicotine metabolism. <sup>114</sup> Acknowledges funding from the STRC.
Apr 1994	Idle, Daly and others at Newcastle publish a paper in <i>Pharmacogenetics</i> with their Norwegian collaborators, reporting no significant link between genetic variations in CYP2D6 and lung cancer. <sup>115</sup> Acknowledges CTR funding.
Apr 1994	Idle, Daly and colleagues at Newcastle publish another paper in <i>Pharmacogenetics</i> investigating whether newly discovered CYP2D6 mutations could explain discrepancies between genetic test results and debrisoquine metabolism. <sup>116</sup> Acknowledges BAT funding.
Apr 1994	Wolf <i>et al.</i> 's response to Idle <i>et al.</i> 's 1992 review is published in <i>Pharmacogenetics</i> (it was submitted in Jan 1993). <sup>117</sup> They express concerns that Idle's article is "factually misleading" and that his "strong opinions...are preventing proper, scientifically correct analysis of the available data". Idle and others respond (no tobacco funding is acknowledged). <sup>118</sup>
25 Apr 1994	CTR refuses Idle funding for his proposed further project. <sup>119</sup>
Jun 1994	Idle and Daly co-author a paper in <i>Pharmacogenetics</i> <sup>120</sup> reporting on the frequency of 'poor metabolisers' in Jordan. BAT funding acknowledged.
7 Jul 1994	Idle and Daly's final report to BAT. <sup>121</sup>
Nov 1994	Daly, Idle co-author a review of metabolism genes and disease susceptibility. <sup>122</sup>
Mar 1995	Daly, Idle, London and others publish a new mutation in the CYP2D6 gene. <sup>123</sup> Acknowledges funding from BAT and the CTR.
Aug 1995	Idle and Daly co-author a paper in <i>Pharmacogenetics</i> , discussing how to improve the accuracy of CYP2D6 genetic testing. <sup>124</sup> BAT funding acknowledged.
Aug 1995	Idle and Daly co-author a paper in <i>Pharmacogenetics</i> on CYP2D6 and NNK activation (which concludes that this is not important) <sup>125</sup> . No funding acknowledgements.
Aug 1995	London, Daly and Idle investigate lung cancer risk and genetic variations in GSTM1. <sup>126</sup> They find no link with lung cancer risk overall, but suggest there might be a link for lighter smokers. CTR funding is acknowledged.
16 Jun 1995	Idle and Gonzalez (co-editor of <i>Pharmacogenetics</i> ) named as inventors on a US patent for CYP2C9 and CYP2A6 test kits (granted on 6 April 1999). <sup>127</sup> The description claims that CYP2A6 is linked to lung cancer risk.
Sep 1995	Idle co-authors a paper on genetic variations in CYP2A6 and suggests it is linked to both cancer susceptibility and nicotine metabolism. <sup>128</sup>
Nov 1995	Daly publishes a paper reviewing drug metabolism, which admits that links between CYP2D6 and lung cancer are controversial. <sup>129</sup>

Late 1995	Smith <i>et al.</i> <sup>130</sup> publish a review of genetic variability and cancer susceptibility. They conclude that the role of CYP2D6 remains unclear and that the original strong associations have not been confirmed.
Dec 1995	London, Idle and Daly co-author a paper which reports that CYP1A1 does not appear to affect lung cancer risk <sup>131</sup> . No tobacco industry funding is acknowledged.
Dec 1995	Idle co-authors a paper which advocates genetic screening for drug metabolism. <sup>132</sup>
Dec 1995	NCI researchers (in <i>Pharmacogenetics</i> ) consider possible explanations for some studies finding no link between lung cancer risk and CYP2D6 <sup>133</sup> . Includes Fisher's hypothesis as one possible explanation.
15 Dec 1995	Idle moves to the Norwegian University of Science and Technology in Trondheim.
1 Jan 1996	BAT begins payments for Daly's project on CYP1A2 and CYP2E1. <sup>134</sup>
Apr 1996	London, Daly and Idle co-author a paper finding no link between CYP2E1 and lung cancer risk. <sup>135</sup> Support from CTR acknowledged.
Jun 1996	Idle (now at Trondheim) and co-workers at Newcastle publish a paper in <i>Pharmacogenetics</i> on CYP2D6 and smoking status, finding no link. <sup>136</sup> Support from the STRC is acknowledged.
19 Aug 1996	Idle and Daly co-author a paper describing an improved genetic test for CYP2D6. No tobacco funding acknowledged. <sup>137</sup>
Aug 1996	Daly and Idle co-author a paper reporting improved detection of some genetic variations in CYP2D6 (in <i>Pharmacogenetics</i> ). <sup>138</sup> Acknowledges support from BAT and the CTR.
Sep 1996	Daly, Idle and others review the methods of detection of mutations in CYP2D6. <sup>139</sup> No funding acknowledgements.
Dec 1996	London, Idle and Daly co-author a paper in <i>Pharmacogenetics</i> , finding no link between CYP2C9 and lung cancer risk. <sup>140</sup> CTR acknowledged.
Jan 1997	A meta-analysis of studies on CYP2D6 and lung cancer susceptibility is published. <sup>141</sup> finding no association and concluding that "the quality of the studies left much to be desired".
Apr 1997	Idle and Daly are co-authors on a paper finding two new variants in CYP2D6. <sup>142</sup> (published in <i>Pharmacogenetics</i> ). No tobacco funding acknowledged.
Jun 1997	London, Daly, Idle and co-workers publish a paper on the CYP2D6 Los Angeles study. <sup>143</sup> Concludes that polymorphisms in CYP2D6 are not a strong risk factor for lung cancer. Acknowledges CTR.
Sep 1997	Idle co-authors a paper on CYP2A6 metabolism. <sup>144</sup> No funding acknowledgements.
Oct 1997	Idle and former colleagues at Newcastle publish a paper in <i>Pharmacogenetics</i> on smoking behaviour and CYP2D6 genotype, concluding that it may influence 'dependence'. <sup>145</sup> Acknowledges STRC.
Oct 1997	London, Daly, Idle co-author a paper in <i>Pharmacogenetics</i> on lung cancer risk and CYP2C9. <sup>146</sup> They find no link. No tobacco funding acknowledged.
Feb 1998	A paper by a French team finding no association between CYP2D6 and lung cancer susceptibility is published in <i>Pharmacogenetic</i> . <sup>147</sup>
Mar 1998	NCI researchers conclude that CYP2D6 is not a marker for lung cancer risk but "the concept that genetic polymorphisms may contribute to differential cancer risk is sound". <sup>148</sup>
Apr 1998	Cholerton and co-workers at Newcastle publish a paper on the lack of association between a genetic variation in the DRD2 gene and cigarette smoking. <sup>149</sup> They acknowledge part funding by BAT.
Jun 1998	A meta-analysis of studies on CYP2D6 is published in <i>Pharmacogenetics</i> by a team at Sheffield University. <sup>150</sup> They conclude that there may be a small difference in risk but "it is hard to justify further studies".
Jul 1998	Idle co-authors a paper on CYP2A6 metabolism <sup>151</sup> . Acknowledges support from Rothmans International Services Ltd and the United States Tobacco Company Ltd.
Dec 1998	Idle, London, Daly co-author a paper in <i>Pharmacogenetics</i> , on the CYP2D6 Los Angeles study. <sup>152</sup> It attempts to find a better correlation by including some rarer mutations (but does not succeed). Part funding from the CTR acknowledged.
Dec 1998	Daly and co-authors publish a paper on genetic variations in CYP2E1 (they find none of functional significance). <sup>153</sup> They acknowledge BAT funding.
Dec 1998	Daly co-authors a paper which concludes that CYP2D6 studies have not been confirmed but that CYP1A1 and CYP2E1 are of possible functional significance. <sup>154</sup>



13 Mar 1999	London (now at the US National Institute of Environmental Health), Idle, Daly and a co-author publish a paper in the <i>Lancet</i> on CYP2A6. <sup>155</sup> They find no significant link with lung cancer risk or smoking habits. No tobacco funding acknowledged.
12 Jun 1999	Idle (now based in the Czech Republic) letter to the <i>Lancet</i> saying he differs with his co-authors on the paper. <sup>43</sup>
Mar 2000	A meta-analysis of studies of genetic variations in CYP1A1 and lung cancer risk is published in <i>Pharmacogenetics</i> , finding no link. <sup>156</sup>
Jun 2002	Idle is a co-author on a paper finding that debrisoquine metabolism is influenced by CYP1A1 as well as CYP2D6 and proposing this as the reason for the discrepancies between studies. <sup>157</sup> Acknowledges a travel grant for Idle from the STRC.

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### S3: Rothschild chronology

1977-1981	Rothschild funded for CTR "Special Project 91". <sup>1,2</sup> Total funding: \$121,821. <sup>3</sup>
Feb 1982	CTR lawyers recommend a further \$25,000 for Rothschild to look at " <i>genetic aspects of lung cancer</i> ". <sup>4</sup>
Mar 1982	Rothschild gives evidence for the tobacco industry at the Waxman hearings, arguing that genetics may determine who gets lung cancer. <sup>5</sup>
Apr 1982	Rothschild's funding for CTR "Special Project #118" is approved. <sup>6</sup>
7 Jun 1983	Rothschild receives approval for a further \$34,359 to extend CTR Special Project #118. <sup>7</sup>
Feb 1986	Rothschild co-authors a paper claiming to support the existence of " <i>a susceptibility gene to lung cancer</i> ". <sup>8</sup> No funding acknowledgments.
28 Aug 1986	CTR approves \$48,764 further funding for Rothschild's "Special Project #138". <sup>9</sup>
Oct 1986	Correction to Feb 1986 paper published. <sup>10</sup>
1 Aug 1987	Rothschild co-authors another paper claiming to support the hypothesis of genetic susceptibility to lung cancer. <sup>11</sup> Funding acknowledgments do not include the CTR.
12 Jan 1988	CTR approves another \$52,582 for Rothschild's "Special Project No. 138-A". <sup>12</sup>
Nov/Dec 1988	Rothschild co-authors another paper suggesting lung cancer susceptibility may also increase risk of other cancers. <sup>13</sup> CTR not included in funding acknowledgements.
Aug 1990	Rothschild is a co-author on the JNCI paper Sellers <i>et al.</i> (1990), which gains extensive press coverage for supposedly identifying a genetic factor in lung cancer [see Idle chronology].
1991	BAT begin funding Springall to reproduce Sellers <i>et al.</i> 's results. Springall receives £72,700 over three years.
1 Jan 1992	Rothschild co-authors a paper which finds that family history of lung cancer does not appear to differ with cancer type. <sup>14</sup> Part funding from CTR acknowledged.
1 May 1992	Rothschild co-authors a further paper on evidence for an interaction between smoking and genetic predisposition to lung cancer. <sup>15</sup> No funding acknowledgements.
5-7 May 1992	The SRG minutes note that Springall and Lee have purchased Rothschild's dataset (for £25,000 <sup>16</sup> ) but are having difficulty reproducing Sellers <i>et al.</i> and "are concerned his model may be the wrong one." <sup>17</sup>
Jul/Aug 1992	Rothschild is a co-author on another paper suggesting that "the genetic component of lung cancer may be greater than previously estimated", although the paper concludes that it is premature to suggest genetic screening. <sup>18</sup> No funding acknowledgements.
April 1993	Rothschild is a co-author on another paper which claims to provide evidence that a genetic factor may affect the risk of lung cancer. <sup>19</sup> Part funding from the CTR is acknowledged.
7-9 June 1993	The SRG reports that Springall has successfully reproduced Sellers <i>et al.</i> and that a proposal has been submitted from the Sellers group to the SRG. <sup>20</sup>
Oct 1993	Rothschild's colleague JE Bailey-Wilson presents their proposal. <sup>21</sup> Rothschild's project then listed as a new project approved, under the name of another colleague: R Elston. <sup>22</sup>
Jan 1994	SRG begin funding Rothschild and colleagues for a 3-year project on the genetics of lung cancer " <i>pending funding by the NIH</i> " (£118,000 in total). <sup>23</sup>
Sept 1994	Rothschild co-authors another paper on genetic susceptibility to "smoking-associated cancers". <sup>24</sup> No tobacco funding acknowledged.
2000	Rothschild receives 3 grants (total \$660,000) from the NIH to study genetic susceptibility to lung cancer. <sup>25</sup>

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#### S4: Genetic damage chronology

Date	Notes
1987	BAT begins funding Currie's project on p53 and lung cancer at the Marie Curie Research Institute. The project receives £240,000 over 8 years to the end of 1993. <sup>1</sup>
1990	The first paper suggesting a link between p53 mutations in lung cancer cells and tobacco smoke is published (Chiba et al, 1990). <sup>2</sup> A copy in Philip Morris' files contains the added handwritten comment " <i>No association of p53 mutations and smoking</i> ". <sup>3</sup>
Sep 1991	BAT visit Graham Currie and John Jenkins at the Marie Curie Research Institute. <sup>4</sup>
Undated (1991)	Field and Stell's research proposal to BAT <sup>5</sup> . They say that the p53 mutation pattern in lung cancer adds weight to the association between smoking and lung cancer. They plan to look at p53 mutations in head and neck cancers. <sup>6</sup>
Oct 1991	Funding for Stell and Field's project begins.
Feb 1992	Field et al (1992). <sup>7</sup>
1992	List of SRG research projects <sup>8</sup> including brief summaries of Field and Currie's projects on p53 and Clausen's on adduct levels in smokers and non-smokers and the effect of dietary antioxidants.
May 1992	SRG meeting. <sup>9</sup> Notes p53 mutation spectra as an "important area". Expresses doubts about Field but notes Jenkins' advice is helpful. Notes that Clausen "has found the adduct levels of smokers and non-smokers to be comparable".
Jun 1992	SRG visit to the Thrombosis Research Institute in London. <sup>10</sup> <i>"The SRG's interest in Dr Cooper's project stems from the possibility that mutations in protein C (leading to various forms of thrombosis) might be similar to those in mutated proteins associated with other diseases, on the basis that DNA is most likely to mutate at specific sites and not at random. The extent to which the spectrum of inherited mutations that arise in, for example, the p53 isolated from lung cancer cells is a matter of interest and would clearly have a bearing in assessing the importance of environmental chemicals in causing mutations."</i> BAT also meet Professor Kakkar, Director of the Unit.
Jul 1992	Field(1992). <sup>11</sup>
Aug 1992	BAT funding for David Cooper's project begins.
Aug 1992	Skaanild and Clausen (1992). <sup>12</sup> No funding acknowledgements.
Mar 1993	Slingerland et al (1993). <sup>13</sup> John Jenkins is a co-author. Emphasises the role of selection of p53 mutations during tumour progression. Acknowledges funding from the National Cancer Institute of Canada and the Medical Research Council of Canada.
Apr 1993	BAT funding begins for Peter Farmer's project comparing genetic damage in smokers and non-smokers. <sup>14</sup>
May 1993	Field co-authors a paper which highlights the link p53 mutations and cigarette smoke. <sup>15</sup>
May 1993	Spandidos et al(1993). <sup>16</sup> Field is a co-author.
Jun 1993	SRG meeting <sup>17</sup> . Although Cooper's project is entitled "Mutations in thrombotic disease", BAT notes: " <i>Dr Cooper is comparing the types of mutations inherited in the germline with those found in p53 genes isolated from tumour tissue. The considerable similarities suggest that p53 mutation spectra are mainly dependent on the position and sequence of the DNA.</i> "
Aug 1993	Clausen, J (1993). <sup>18</sup>

5-6 Sep 1993	BAT visit to Mohr and Krawczak in Germany. <sup>19</sup> Records that Ulrich Mohr has now accepted the invitation to become a consultant to the SRG. <i>"Dr Krawczak works in collaboration with Dr DN Cooper (supported by BAT at the Thrombosis Research Unit). They are both interested in Human Genetics and met when both worked for Professor Schmitke in Gottingen. Professor Schmitke has now moved to Hannover. Krawczak and Cooper have shown, for example, the nucleotide sequence -C-G- is inherently unstable after methylation (which occurs naturally in vertebrates)...causing a G-A transition in the complementary strand. They have now compared mutations in p53 derived from somatic cells (i.e. cancer derived) with mutations in p53 derived from germ-line cells...88% homology is claimed, suggesting that most mutations in p53 in somatic cells are the result of genetic instability rather than being caused by environmental chemicals. Unfortunately the paper on this subject submitted to 'Nature' has been rejected out of hand, probably as too revolutionary. It will now be submitted to 'Science'."</i>
Oct 1993	Field is lead author on a review paper discussing p53 mutations in lung cancer and head and neck cancer. <sup>20</sup> He again contradicts BAT's position.
Oct 1993	SRG meeting. <sup>21</sup> The SRG discuss David Cooper's research on "Mutational spectra of somatic disease". <i>"Dr Cooper compared somatic gene mutations from a database of tumour-derived p53, to his own database of inherited germline mutations which are thought to arise spontaneously rather than as a result of environmental factors. The distribution of mutation types was found to be similar in the two databases, although G to T transversions were more common in the tumour samples. Dr Cooper stated that the vast bulk of mutations are formed by endogenous processes, and that it is impossible to determine the cause of a single mutation in an individual."</i>
Dec 1993	BAT's RE Thornton writes a note for the Tobacco Strategy Group, summarising the SRG's October meeting. <sup>22</sup> Thornton notes "Dr Cooper's work, originally targeted at the genetic basis of thrombotic disorders had turned out to be widely applicable and relevant to a number of diseases. Specifically, he was now examining the applicability of his ideas on spontaneously occurring genetic mutations to cancer."
Feb 1994	Field applies for renewal of his SRG grant. <sup>23</sup>
Mar 1994	The SRG decides that further funding for Field's project is "low priority". <sup>24</sup>
Jun 1994	Tavares et al (1994). <sup>25</sup> Farmer is a co-author. <i>"The [adduct] concentrations in the newborns from smoking mothers...was significantly higher...than the concentrations in the newborns from non-smoking mothers."</i>
1994	Field et al (1994). <sup>26</sup>
Jul 1994	Field is a co-author on a paper which claims to have identified a new predisposing gene for head and neck cancers. <sup>27</sup>
Jul 1994	Farmer(1994). <sup>28</sup>
20-21 Sep 1994	SRG meeting, Hamburg. <sup>29</sup> Notes that Farmer's two PhD students will look at adducts and oxidative damage in smokers and non-smokers.
Jan 1995	Field (1995). <sup>30</sup>
Feb 1995	Summary of research projects funded by the SRG in 1995.
24-25 Apr 1995	SRG meeting, Århus. <sup>31</sup> <i>"Dr Cooper would be offered a donation to his research group in return for occasional presentations to the SRG on the state of current science in his field of expertise. The exact nature of the contract will be discussed with Dr Cooper but may provide a basis for similar arrangements with other scientists."</i> Also reports BAT's receipt of the first year report from Farmer's second PhD student.
16 Mar 1995	Brennan et al (1995). <sup>32</sup> Scientists at John Hopkins Medical Center report "molecular proof that smoking increases the rate of mutation" in the p53 gene". <sup>33</sup> . The Tobacco Institute tells the <i>Los Angeles Times</i> "The Tobacco Institute does not have the sophisticated resources necessary to evaluate research on gene mutation theories."

1995	Krawczak et al (1995). Vijay Kakkar and David Cooper, of the Thrombosis Research Institute, are co-authors. <sup>34</sup> “...we have demonstrated here that the bulk of the spectrum of somatic single basepair substitutions in the TP53 gene strongly resembles that of their germline counterparts seen in other human genes...it would appear that many TP53 mutations in the soma may have arisen directly or indirectly as a consequence of endogenous cellular mechanisms (perhaps including those involved in DNA repair and replication) rather than through the action of exogenous mutagens.” Funding is acknowledged from the Norwegian Cancer Association and Charter Consolidated PLC.
20 Mar 1995	A BAT memo to SRG members <sup>35</sup> outlines the findings in Brennan <i>et al</i> (1995). The memo claims that: “The mutations did not necessarily cause the cancer” and “Overall, in our opinion this study does not establish a causal link between smoking and cancer.” The memo gives one reference – Krawczak <i>et al.</i> (1995).
Jul 1995	Poulsen & Loft (1995). The paper suggests that “oxygen species” can cause identical DNA damage to external chemicals (xenobiotics), such as those in tobacco smoke.
Dec 1995	Farmer (1995). <sup>36</sup> The paper emphasises that genetic damage (DNA adducts) could be formed by internal mechanisms (endogenous processes) rather than by exposure to cancer-causing chemicals.
1996	Lawrence <i>et al</i> (1996). <sup>37</sup> Farmer is a co-author. Describes a method for measuring adduct levels. Funding from the UK MRC and from the Commission of European Communities.
May 1996	Farmer <i>et al</i> (1996). <sup>38</sup> Finds “adduct levels in smokers were significantly higher than those in nonsmokers”.
Jun 1996	Loft & Poulsen (1996). <sup>39</sup> A review of cancer risk and oxidative DNA damage. The paper notes oxidative damage to DNA increases with age and that both ionizing radiation and smoking can increase damage rates. Suggests protective effects from eating Brussels sprouts, increasing vitamin C or eating a low-fat diet.
Jul 1996	Farmer et al (1996). <sup>40</sup>
Jul 1996	Lykkesfeldt et al (1996). <sup>41</sup> Poulsen is a co-author. “These results...strongly suggest that the low ascorbic acid concentrations in [smokers’] plasma related to smoking per se” [rather than diet]. Acknowledges funding from BAT and the Danish Environmental Research Programme.
Aug 1996	Poulsen et al (1996). “ <i>Oxidative stress to DNA points to a risk for the development of cancer and premature ageing from extreme exercise.</i> ”
Jul 1998	Discussion Forum by Krawczak and Cooper is published in the journal <i>Mutagenesis</i> (of which James Parry is the editor). <sup>42</sup>
Aug 1998	Philip Morris document re Parry’s “long-standing relationship” with them and his proposal for future work on (i) mutation spectra and (ii) genetic susceptibility. <sup>43</sup> PM had previously funded Parry in 1996 to compare the effects of environmental hazards on the respiratory tract (including passive smoking, diesel fumes and urban pollution). <sup>44, 45</sup>
Nov 1998	Pfeifer et al (1998). <sup>46</sup> Response to the <i>Mutagenesis</i> Discussion Forum. Describes Krawczak and Cooper’s main argument as “erroneous and misleading”.
Mar 1999	Farmer & Shuker (1999). <sup>47</sup>
Nov 2000	Paschke (2000) published in <i>Mutagenesis</i> . <sup>48</sup> Claims no significant differences between p53 sequences in smoking and non-smoking lung cancer patients.
Nov 2000 to Mar 2001	Exchange of letters between Hainaut and Parry regarding the failure to declare tobacco funding of Paschke’s research institution [Personal communication].
Nov 2001	Hainaut et al’s reply to the Paschke’s article, <sup>49</sup> together with a response from Paschke <sup>50</sup> , are published in <i>Mutagenesis</i> . Paschke now declares tobacco funding.
Nov 2001	The last issue of <i>Mutagenesis</i> with Parry as editor in chief. The journal adopts a new policy on conflicts of interest. <sup>51</sup> However, Parry remains on the editorial board and also becomes acting editor of the <i>European Journal of Genetic and Molecular Toxicology</i> . <sup>52</sup>
Jun 2002	Lewis <i>et al</i> (2002). <sup>53</sup> Parry is a co-author. The paper claims there is no difference in mtDNA mutations between smokers and non-smokers.

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